IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC.,	)	Redacted - Public Version
Plaintiff,	)	[redacted]
v.	)	C.A. No. 18-651-CFC
	)	**ANDA CASE**
TEVA PHARMACEUTICALS USA, INC., et al.	)	**CONSOLIDATED**
Defendants.	)	

DEFENDANTS' RESPONSIVE PROPOSED FINDINGS OF FACT

Thomas Francella (No. 3835)
Kaan Ekiner (No. 5607)
COZEN O'CONNOR
1201 North Market Street, Suite 1001
Wilmington, DE 19801
(302) 295-2025
tfrancella@cozen.com
kekiner@cozen.com
Attorneys for Defendants Apotex Inc. and Apotex Corp.

OF COUNSEL:
Barry P. Golob
W. Blake Coblentz
Aaron S. Lukas
COZEN O'CONNOR
1200 Nineteenth Street N.W.
Washington, DC 20036
(202) 912-4800

John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
Andrew E. Russell (No. 5382)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street
12th Floor
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
arussell@shawkeller.com
nhoeschen@shawkeller.com
Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

Keri L. Schaubert
COZEN O'CONNOR
3 WTC, 175 Greenwich Street
55th Fl.
New York, NY 10007
(212) 509-9400

OF COUNSEL:
J.C. Rozendaal
Deirdre M. Wells
William H. Milliken
Sasha Rao
Michael Bruns
Byron L. Pickard
STERNE, KESSLER, GOLDSTEIN
& FOX P.L.L.C.
1100 New York Avenue, N.W.
Suite 600
Washington, DC 20005
(202) 371-2600

Dated: May 17, 2022

TABLE OF CONTENTS

RESPONSIVE PROPOSED FINDINGS OF FACT

Defendants Teva Pharmaceuticals USA, Inc., Apotex Inc., and Apotex Corp. hereby submit the following Post-Trial Responsive Proposed Findings of Fact based on the testimony of fact and expert witnesses and exhibits admitted at trial.

I. Witnesses

A. Defendants' Expert Witnesses

1. Dr. Deborah Jaskot

1. The parties do not dispute Ms. Jaskot is an expert in the field of FDA regulatory law and the FDA drug approval process. D.I. 299 ¶ 1; Tr. 396:7-12.

2. Mr. Jaskot is currently an independent pharmaceutical consultant providing regulatory advice to a broad range of clients, including both generic and brand pharmaceutical companies. Tr. 397:2-8.

3. Prior to her work as an independent consultant, Ms. Jaskot worked for both Sandoz (formerly Cord Laboratories) and Teva Pharmaceuticals USA. Tr. 397:13-20; DTX-399.1.

4. Ms. Jaskot began as a regulatory affairs associate at Teva in 1989, and moved through a series of progressively more senior positions, ending her career at Teva as the Vice President of U.S. Generic Regulatory Affairs and North American Policy. Tr. 397:16-20; DTX-399.1.

5. During her tenure at Teva, Ms. Jaskot was the primary liaison between Teva and FDA, in particular, the Office of Generic Drugs and the Office of Pharmaceutical Science. Tr. 398:16-20; DTX-399.1, 399.2.

6. As part of her responsibilities at Teva, Ms. Jaskot routinely reviewed marketing materials to ensure such materials complied with FDA regulations. Tr. 398:21-399:2.

7. Over the course of her career, Ms. Jaskot ushered hundreds of drug applications through the FDA approval process. Tr. 398:7-15.

2. Dr. John Winkelman

8. The parties do not dispute Dr. Winkelman is an expert in his field. D.I. 299 ¶ 1; Tr. 494:16-19.

9. Dr. Winkelman is currently a professor of psychiatry at Harvard Medical School, and chief of the Sleep Disorders Clinical Research program at Massachusetts General Hospital. Tr. 493:15-17; DTX-402.2.

10. Dr. Winkelman's research concerns sleep disorders, insomnia, parasomnia, restless leg syndrome and their relationship to psychiatric illness, neurological disease and general medical disorders. Tr. 493:18-494:8.

11. Dr. Winkelman received a bachelor's degree in psychobiology from Williams College in 1978, a Ph.D. in Psychobiology from Harvard University in

1983, and a medical degree from Harvard University in 1987. Tr. 493:6-12; DTX-402.1.

12. Dr. Winkelman has been a practicing sleep medicine physician for 30 years, treating patients with a variety of circadian rhythm disorders. Tr. 494:9-15.

II. Defendants will not induce infringement of the asserted claims of the RE604, '829, and '910 patents.

A. RE604 patent

13. Defendants' labels will not induce infringement of claim 3 of the RE604 patent. Tr. 496:6-25, 498:6-16, 511:6-20 (Winkelman).

1. "A method of entraining a patient suffering from Non-24 to a 24 hour sleep-wake cycle"

14. Defendants' labels do not instruct, encourage, promote, teach, or recommend that prescribers practice a method of entraining a patient suffering from Non-24 to a 24-hour sleep-wake cycle. Tr. 496:6-25, 498:9-16, 501:15-22, 504:19-25 (Winkelman); JTX-030; JTX-33.

15. The accused labels do not include the words entrain, entraining, entrainment, synchronize, or synchronizing. Tr. 240:23-241:2 (Combs); Tr. 496:6-11 (Winkelman); Tr. 162:8-11, 167:2-8 (Polymeropoulos); Tr. 445:12-16 (Jaskot).

16. Prescribers understand that one can treat the symptoms of a disease (*e.g.*, sleep disturbances) or the underlying cause of the disease (*e.g.*, lack of entrainment). Tr. 496:18-497:7 (Winkelman).

17. Sleep disturbances (*e.g.*, decreased nighttime sleep and increased daytime sleep) are a key characteristic of Non-24, and the primary reason why patients often seek treatment. Tr. 496:18-25, 498:14-16 (Winkelman); Tr. 465:10-11 (Dressman); Tr. 160:23-161:4 (Polymeropoulos).

18. Section 1 (the Indication and Usage section) of Defendants' labels states: "Tasimelteon capsules are indicated for the treatment of Non-24 in adults." JTX-30.2, JTX-33.3.

19. Some Non-24 patients treated with tasimelteon will experience improved sleep—that is, symptomatic treatment—without entrainment. Tr. 509:4-511:5 (Winkelman); Tr. 466:6-22 (Dressman); JTX-1.33 (Tables 1A and 1B).

20. Section 2.2 (the Dosage and Administration section) of Defendants' labels states: "The recommended dosage of tasimelteon capsules in adults is 20 mg one hour before bedtime, at the same time every night." JTX-30.2, JTX-33.3.

21. Section 2.4 (the Dosage and Administration section) of Defendants' labels states: "If a patient is unable to take tasimelteon capsules at approximately the same time on a given night, they should skip that dose and take the next dose as scheduled." *Id*.

22. The instructions in §§ 2.2 and 2.4 were included in Defendants' labels because they reflect the protocol used in the pivotal clinical studies (Study 3201 (the SET study) and Study 3203 (the RESET study)) that supported the approval of

Hetlioz for the treatment of Non-24. Tr. 500:1-5, 550:18-551:10 (Winkelman); PTX-815.37, 815.38. These clinical trials measured both sleep parameters (nighttime total sleep time on the worst 25% of nights and daytime sleep time on the worst 25% of days) and entrainment parameters (aMT6 and cortisol levels). Tr. 551:11-16 (Winkelman); PTX-815.19.

23. The entrainment parameters (*e.g.*, aMT6 and cortisol levels) from the clinical study protocol are not included in Defendants' labels. Tr. 551:11-19 (Winkelman).

24. A prescriber would understand that one of the effects of tasimelteon is to induce sleepiness. Tr. 1210:24-1211:1 (Czeisler).

25. A prescriber would understand that one might want to make 20 mg of tasimelteon near bedtime to take advantage of the soporific effect (*i.e.*, sleep-inducing effect) that tasimelteon has. Tr. 1211:2-6 (Czeisler).

26. Section 5.1 (Somnolence) of Defendants' labels states: "After taking tasimelteon capsules, patients should limit their activity to preparing for going to bed. Tasimelteon can potentially impair the performance of activities requiring complete mental alertness." JTX-30.2; JTX-33.3; Tr. 502:4-17 (Winkelman). A prescriber would understand that this is a warning that the patient may experience increased sleepiness (somnolence) after administration of tasimelteon, which is consistent with the clinical trial results reported in the labels. Tr. 502:4-17

(Winkelman). A prescriber would understand that this warning is similar to the warnings and precautions that one would see in the label for hypnotic agents such as Ambien, Lunesta, and Rozerem. *Id*.

27. Section 14.1 (the Clinical Studies section) of Defendants' labels discuss the results of the two pivotal clinical trials that supported the FDA approval of Hetlioz, Study 1 (the SET study, Study 3201) and Study 2 (the RESET study, Study 3203). JTX-30.8, 30.9; JTX-33.10, 33.11; Tr. 499:13-500:5 (Winkelman). Section 14.1 states: "Study 1 and Study 2 evaluated the duration and timing of nighttime sleep and daytime naps via patient-recorded diaries." JTX-30.9, JTX-33.11. Section 14.1 discloses that the two sleep-measure outcomes (the duration and timing of nighttime sleep and daytime naps) were based on "the 25% of nights with the least nighttime sleep, and the 25% of days with the most daytime nap time." JTX-30.8, 30.9; JTX-33.10, 33.11; Tr. 500:11-501:1 (Winkelman).

28. A prescriber would understand that the endpoints of Studies 1 and 2 are measures of tasimelteon's effect on two symptoms of Non-24, *i.e.*, poor sleep on certain nights and increased sleep during certain days—not entrainment. Tr. 499:3-22, 500:11-501:1, 501:9-14, 503:3-504:25 (Winkelman).

29. Regarding Study 2, the accused labels disclose: "[p]atients in whom the calculated time of peak melatonin level (melatonin acrophase) occurred at approximately the same time of day (in contrast to the expected daily delay) during

the run-in phase were randomized to receive placebo or continue treatment with tasimelteon 20 mg for 8 weeks." JTX-30.8, 30.9; JTX-33.10, 33.11. A prescriber would recognize that despite the reference to melatonin acrophase, no data related to melatonin levels is present in the accused labels. Tr. 499:3-22, 500:18-501:1, 501:15-22, 503:15-22, 552:8-18 (Winkelman); Tr. 165:13-24 (Polymeropoulos); Tr. 240:16-22 (Combs); JTX-30.9; JTX-33.11.

30. Prescribers would understand that the only results presented in Defendants' labels for Studies 1 and 2 concern sleep parameters—increased nighttime sleep and decreased daytime sleep. Tr. 499:3-22, 500:11-17, 500:21-501:1, 501:9-14 (Winkelman); Tr. 165:13-24 (Polymeropoulos); JTX-30.9; JTX-33.11.

31. Prescribers would understand that one cannot determine if a patient is entrained just by looking at a patient's nighttime sleep duration and daytime sleep duration. Tr. 162:12-21 (Polymeropoulos); Tr. 484:9-15 (Feeney).

32. As set forth in § 14.1, "[i]n Study 1, patients in the tasimelteon group had, at baseline, an average 195 minutes [3 hours and 15 minutes] of nighttime sleep and 137 minutes of daytime nap time on the 25% of most symptomatic nights and days, respectively." JTX-30.9; JTX-33.11. Table 3 shows that patients receiving tasimelteon slept on average 50 minutes more per night on their worst 25% of nights (for a total average nighttime sleep time of 4 hours and 5 minutes), and had a 49

minute decrease in daytime nap time on their worst 25% of days. JTX-30.9; JTX-33.11; Tr. 500:11-17 (Winkelman).

33. The metrics presented in Table 3 are clinical endpoints (*i.e.*, sleep parameters) that are not markers of entrainment. Tr. 499:3-22, 501:9-22, 504:3-25 (Winkelman).

34. In its clinical trial protocol for Study 1 (the SET study), Vanda distinguished entrainment endpoints from sleep endpoints. Tr. 505:2-18, 506:7-507:3, 508:2-509:3 (Winkelman).

35. In the Study Objectives section of the clinical trial protocol, Vanda referred to "[e]ntrainment of the 6-sulfatoxymelatonin (aMT6s) rhythm" when discussing the Primary Objective. PTX-815.19; Tr. 506:7-20 (Winkelman).

36. Vanda referred to "entrainment as assessed by urinary cortisol" in its Secondary Objectives. JTX-815.19; Tr. 508:14-18 (Winkelman). Conversely, when discussing increased nighttime total sleep time in the lower quartile of nights ("LQ-nTST") and decreased daytime sleep duration in the upper quartile of days ("UQ-dTSD") in the Secondary Objectives section of the clinical trial protocol, Vanda did not use the term entrainment. PTX-815.19; Tr. 508:3-13, 508:19-509:3 (Winkelman).

37. If the accused labels encouraged treatment of Non-24 by entraining a patient suffering from Non-24 to a 24 hour sleep-wake cycle, a prescriber would

expect to see data related to melatonin or cortisol levels—markers of entrainment—in the labels. Tr. 501:15-22 (Winkelman).

38. No such data is present in the accused labels. *Id*.

39. Vanda attempted to include entrainment endpoints, *i.e.*, aMT6 levels and urinary cortisol levels, in its label, but FDA did not permit Vanda to rely on entrainment as a surrogate endpoint. Tr. 401:23-402:7 (Jaskot).

40. During the course of regulatory approval of Hetlioz, there were negotiations between FDA and Vanda about appropriate endpoints for the clinical trials necessary to support the "treatment of Non-24" indication for Hetlioz. Tr. 400:9-25, 401:20-402:7 (Jaskot).

41. Clinical trial endpoints include primary endpoints, which demonstrate a clinical benefit (*i.e.*, affect the patient's functions, feelings and survival), and secondary endpoints, which are supportive information, but do not support FDA approval. Tr. 401:7-19 (Jaskot). Surrogate endpoints, on the other hand, are substitutes for measuring an actual clinical benefit. *Id*.

42. If an indication is based on a surrogate clinical endpoint, FDA regulations require the label to include a statement about reliance on the surrogate endpoint. Tr. 415:8-25 (Jaskot). The Hetlioz label does not include a statement about reliance on a surrogate endpoint because FDA did not approve Hetlioz for the

treatment of Non-24 based on evidence of entrainment (Vanda's proposed surrogate endpoint). Tr. 402:4-7, 415:16-416:3 (Jaskot); Tr. 465:12-466:5 (Dressman).

43. In a January 6, 2011 meeting between FDA and Vanda, FDA stated that it was skeptical that biomarkers (*e.g.*, entrainment based on aMT6s) were well-enough understood to take the place of a clinically meaningful endpoint. JTX-66.3; Tr. 404:13-20 (Jaskot).

44. FDA and Vanda agreed that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit. JTX-66.5; Tr. 405:1-9 (Jaskot).

45. On August 18, 2011, FDA responded to Vanda's request for a Special Protocol Assessment. In response to being asked whether a statistically significant difference between treatment arms for entrainment in Study 3203 (RESET study) in combination with a statistically significant improvement in total nighttime sleep in Study 3201 (SET study) would support the filing of its NDA, FDA responded no, that the use of a biomarker (*i.e.*, entrainment of melatonin circadian rhythms) was a filing issue. Tr. 408:7-25 (Jaskot); JTX-68.57.

46. A filing issue means that FDA has determined that an application is substantively incomplete and does not merit review. Tr. 409:1-13 (Jaskot).

47. Vanda subsequently filed a request to submit its NDA under the Subpart H approval pathway. JTX-69; Tr. 409:14-21, 410:14-16 (Jaskot).

48. Subpart H submission allows for accelerated approval of an application, and can be based on a surrogate endpoint. Tr. 410:8-16 (Jaskot).

49. On June 8, 2012, responding to Vanda's request to submit its NDA as a Subpart H submission, FDA stated: "Subpart H is not an appropriate pathway for approval of tasimelteon in Non 24 because clinical benefit can clearly be shown…." JTX-69.2; Tr. 410:14-411:23 (Jaskot).

50. In November 2012, FDA provided a response to Vanda's Statistical Analysis Plan ("SAP"). Tr. 412:13-18 (Jaskot). FDA reiterated "at least one clinical trial demonstrating efficacy on an appropriate clinical outcome is necessary for the approval of tasimelteon in Non-24 hour sleep-wake disorder (Non-24)," "subpart H approval based on entrainment is not a viable option for filing an NDA," and "use of a biomarker instead of a clinical efficacy endpoint is an NDA filing issue rather than a review issue." JTX-67.1; Tr. 412:13-413:16 (Jaskot).

51. On November 14, 2013, during an FDA advisory meeting, FDA stated that peak production of aMT6s (the major urinary metabolite of melatonin) and cortisol in urine (together, τ) is "not a validated surrogate marker that can be used in lieu of primary clinical outcomes." JTX-110.39; Tr. 414:7-16 (Jaskot).

52. In a Summary Review (JTX-84) prepared after the FDA advisory meeting, the review team recommended approval of Hetlioz for the treatment of Non-24. Tr. 416:4- 417:7 (Jaskot). The reviewer stated that approval was not based

on the biomarker-based endpoints chosen by Vanda (*i.e.*, entrainment), and that the most clinically relevant endpoints for the indication (*i.e.*, treatment of Non-24) were "the duration of nighttime sleep, as assessed by the 'Lower Quartile of Nighttime total sleep time,' and the duration of daytime naps, as assessed by the 'Upper quartile of Daytime total sleep duration.'" Tr. 417:8-418:4 (Jaskot); JTX-84.9.

53. In addition to negotiations with FDA concerning clinical trial endpoints, during the final stages of the regulatory approval process, a drug sponsor must also obtain FDA approval for the drug's labeling. *See* Tr. 419:3-11 (Jaskot).

54. FDA regulations specify what the drug sponsor can and cannot include in the label. Tr. 421:4-6 (Jaskot). For example, the FDA regulation (21 C.F.R. § 201.57(c)(2)) concerning the Indication and Usage section states that only the indication that is supported by substantial evidence of effectiveness can be included in that section. Tr. 421:4-15 (Jaskot). FDA has a reciprocal regulation (21 C.F.R. § 201.57(c)(15)) for the Clinical Trials section, which states that this section cannot imply or suggest indications or uses that are not stated in the Indications and Usage section. Tr. 421:4-18 (Jaskot).

55. During the FDA approval process for Hetlioz, Vanda created a draft label. DTX-139; Tr. 419:12-14 (Jaskot).

56. The draft Hetlioz label includes an extensive discussion of entrainment. Tr. 419:25-420:10, 445:17-22 (Jaskot); Tr. 167:2-8 (Polymeropoulos); DTX-139.

57. The FDA-approved Hetlioz label—available to prescribers and patients—does not include any mention of entrainment. Tr. 418:5-23, 422:13-17 (Jaskot); Tr. 496:6-11, 499:3-10 (Winkelman); Tr. 240:23-241:2 (Combs); Tr. 162:8-11, 167:2-8 (Polymeropoulos); JTX-28.

58. The entrainment language found in the draft Hetlioz label was removed from the FDA-approved Hetlioz label because FDA did not permit Vanda to rely on entrainment as a surrogate endpoint for the "treatment of Non-24." Tr. 401:23-402:7, 420:22-421:3, 422:13-24 (Jaskot); Tr. 167:1-8 (Polymeropoulos); *compare* DTX-139, *with* JTX-28.

59. Because generic labels must be essentially the same as the brand label, and because Vanda was not permitted to use entrainment in its label, neither of Apotex's nor Teva's label can include entrainment. Tr. 423:10-16 (Jaskot).

60. A drug sponsor cannot market a drug for indications or uses that are outside the label. Tr. 422:25-423:4 (Jaskot). Hetlioz was not FDA-approved for entrainment; therefore, Vanda cannot market Hetlioz for entrainment. *Id*.

61. Vanda instructs its sales force that "Entrainment should not be used to convey efficacy of Hetlioz" and that the following terms and phrases should be avoided when marketing Hetlioz:

- "entrain/entrainment," "Hetlioz is a circadian regulator,"

- Non-24 is a circadian rhythm disorder characterized "by lack of entrainment" or "by a shift of the master body clock as it relates to the 24-hour day,"
- "HETLIOZ aligns the master body clock to the 24-hour day," and
- "HETLIOZ aligns circadian rhythms to the 24-hour day."

Tr. 170:12-171:5, 171:20-173:5 (Polymeropoulos); JTX-115.3, 115.7 (Vanda Promotional Messaging Guidebook); JTX-99.2, 99.4 (HETLIOZSolutions™ & Case Management - FIELD USE).

62. Dr. Polymeropoulos, Vanda's CEO, admitted, when discussing the marketing of Hetlioz, that "Vanda would not want to use a word that is not on the label," and that the word entrainment is "not on the label." Tr. 171:6-19.

2. "in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours, and maintaining said 24 hour sleep-wake cycle"

63. Defendants' labels do not instruct, encourage, promote, teach, or recommend to prescribers that "the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours, and maintaining said 24 hour sleep-wake cycle" (the "daily sleep period limitation"). Tr. 511:6-20 (Winkelman); JTX-030; JTX-033.

(a) Plain and ordinary meaning of "a daily sleep period of approximately 7 to 9 hours"

64. The Court construed "a daily sleep period of approximately 7 to 9 hours" to have its plain and ordinary meaning. JPTO, Ex. 1 ¶ 94.

65. A person ordinarily skilled in the art would understand that the plain and ordinary meaning of this term is that "the patient falls asleep at or near a target bedtime and stays mostly asleep for an approximately seven-to-nine-hour period…and then wakes up at the end of that approximately seven-to-nine [hour] period." Tr. 511:23-512:15 (Winkelman); Tr. 802:2-803:6 (Emens) ("a person of skill in the art would assume that this means a person was mostly asleep…they may briefly wake up, but that they would awaken after a period of mostly sleep.").

66. As Dr. Emens explained, "it's described as a period of sleep after which you awaken and not a period of sleepiness after which you arise and get out of bed. So I think the commonsense meaning of that would be that I'd actually slept for some portion of that time." Tr. 802:22-803:1.

67. A daily sleep period is not the same thing as a "sleep opportunity." A sleep opportunity is a common phrase used in sleep medicine, and Vanda chose not to use that term in the claims of the RE604 patent. Tr. 803:2-803:6 (Emens) ("There's a common phrase used in sleep medicine, 'sleep opportunity.' [Vanda] could have used that phrase. That's commonly used, but they didn't. [Vanda

claimed] a period of sleep. So I think the commonsense interpretation would be that they slept."); JTX-1.41 (claims 1-3).

68. The inventors of the RE604 patent viewed the daily sleep period limitation as meaning more than just a sleep opportunity. Tr. 489:21-490:12 (Feeney) (describing the daily sleep period as a "[c]onsolidated period *of sleep lasting* seven-to-nine hours, that occurs in kind of the socially acceptable time frame for that consolidated sleep period") (emphasis added); JTX-13.543 (Dr. Polymeropoulos stating in a declaration to the United States Patent and Trademark Office, "Treatment of Non-24 requires more than just promoting sleep. It requires allowing a patient to fall asleep at approximately his/her target bedtime and to awaken at approximately his/her target wake time following a normal 7-9 hour period of sleep."); Tr. 513:19-514:6 (Winkelman).

(b) Defendants do not infringe the daily sleep period limitation

69. The accused labels do not include the words a "daily sleep period of approximately 7 to 9 hours" or "target wake time." Tr. 161:12-162:7 (Polymeropoulos); Tr. 246:7-10 (Combs); Tr. 514:7-10, 515:15-25 (Winkelman).

70. Sections 1, 2.2, 2.4, and 14.1 of the accused labels do not instruct, encourage, promote, teach, or recommend to prescribers that "the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9

hours, and maintaining said 24 hour sleep-wake cycle." JTX-030; JTX-33; Tr. 515:7-25 (Winkelman).

71. Section 1 of Defendants' labels simply states, "Tasimelteon capsules are indicated for the treatment of Non-24 in adults." JTX-030.2; JTX-33.3.

72. A prescriber would understand that Section 1 of the labels says nothing about awakening at or near a target wake time. Tr. 515:15-18 (Winkelman); Tr. 161:22-162:7 (Polymeropoulos); JTX-30.2; JTX-33.3. Section 1 of the labels does not discuss a sleep period, a sleep opportunity, or the consolidation of sleep into a 7 to 9 hour window after the administration of tasimelteon. Tr. 515:7-25 (Winkelman); Tr. 161:12-21 (Polymeropoulos).

73. Section 2.2 instructs prescribers to administer tasimelteon one hour before bedtime at the same time every night. JTX-30.2, JTX-33.3. Section 2.4 instructs, "If a patient is unable to take tasimelteon capsules at approximately the same time on a given night, they should skip that dose and take the next dose as scheduled." JTX-30.2, JTX-33.3. A prescriber would understand that these sections of the labels say nothing about awakening at or near a target wake time. Tr. 515:15-18 (Winkelman); Tr. 161:22-162:7 (Polymeropoulos); JTX-030.2; JTX-33.3. Nor do these sections discuss a sleep period, a sleep opportunity, or the consolidation of sleep into a 7 to 9 hour window after the administration of tasimelteon. Tr. 515:7-25 (Winkelman); Tr. 161:12-21 (Polymeropoulos).

74. Section 14.1 (Clinical Studies) of Defendants' labels discloses that prior to treatment in Study 1, patients were getting 3 hours and 15 minutes of sleep on the worst 25% of nights. Tr. 514:7-22 (Winkelman). As reported in Table 3, following treatment with tasimelteon, patients slept on average 50 minutes longer (for an average of 4 hours and 5 minutes) on the worst 25% of nights Tr. 514:23-515:4 (Winkelman).

75. A prescriber would understand that 4 hours and 5 minutes is not 7 to 9 hours of sleep. Tr. 514:23-515:6 (Winkelman); *see also* Tr. 490:7-12 (Feeney). A prescriber would recognize that the labels say nothing about when or how long the patients from the clinical trials tried to sleep; they say only that the patients slept on average at least 4 hours and 5 minutes at nighttime. JTX-30.8, 30.9; JTX-33.10, 33.11; Tr. 515:7–25 (Winkelman); Tr. 161:12-162:7 (Polymeropoulos).

76. A prescriber would understand that Defendants' labels do not discuss a hope that patients taking tasimelteon will experience 7 to 9 hours of sleep. Tr. 515:19-21 (Winkelman).

77. A prescriber would understand that Defendants' labels do not state that the goal for treating Non-24 patients with tasimelteon is getting 7 to 9 hours of sleep. Tr. 515:22-25 (Winkelman).

78. To the extent that a daily sleep period is simply an "opportunity" to sleep for 7 to 9 hours, a prescriber would recognize that there is nothing in

Section 14.1, or anywhere in Defendants' labels, about how long patients should set aside for sleep at night. Tr. 515:7-10 (Winkelman).

79. To the extent that a daily sleep period simply requires consolidating sleep into a daily sleep period, a prescriber would recognize that there is nothing in Section 14.1, or anywhere in Defendants' labels, that suggests tasimelteon patients do, or that tasimelteon will cause patients to, consolidate their sleep into one 7 to 9 hour period. Tr. 515:11-14 (Winkelman).

80. A prescriber would understand that Defendants' labels do not provide any information suggesting that taking tasimelteon would cause patients to awaken at or near a target wake time. Tr. 515:15-18 (Winkelman).

B. DDI patents

1. Vanda failed to prove that direct infringement of the DDI patents will likely occur if Defendants' generic tasimelteon products come to market.

81. Asserted claim 14 of the '829 patent depends from claim 13. Claim 13 recites "[a] method of treating patient for a circadian rhythm disorder or for a sleep disorder wherein the patient is being treated with a strong CYP1A2 inhibitor selected from a group consisting of fluvoxamine, ciprofloxacin, and verapamil, the method comprising: (A) discontinuing treatment with the strong CYP1A2 inhibitor and then (B) treating the patient with 20 mg of tasimelteon once daily." JTX-3.35 (38:52-60).

Claim 14 specifies "[t]he method of claim 13, that comprises treating the patient for Non-24-Hour Sleep-Wake Disorder." *Id.* (38:61-62).

82. Claim 1 of the '910 patent recites "[a] method of treating a patient for a circadian rhythm disorder wherein the patient is being treated with rifampicin, the method comprising: (A) discontinuing the rifampicin treatment and then (B) treating the patient with tasimelteon." JTX-4.41 (40:6-15). Asserted claim 4 depends indirectly from claim 1 and adds that the patient is a light-perception impaired patient with Non-24 and that the patient receives 20 mg tasimelteon once daily before a target bedtime. *Id.* (40:16-22).

(a) The evidence showed that prescribers will not directly infringe the DDI patents.

83. Prescribers treating a Non-24 patient who was already being treated with fluvoxamine, verapamil, ciprofloxacin, or rifampicin would not discontinue treating patients with those drugs to begin treatment with tasimelteon. Tr. 519:13-523:5 (Winkelman).

84. Instead, prescribers would continue treating those patients with fluvoxamine, verapamil, ciprofloxacin, or rifampicin and simply not start patients on tasimelteon. *Id.*

85. Fluvoxamine, verapamil, rifampicin, and ciprofloxacin are used to treat patients suffering from a variety of serious bacterial infections, heart-related conditions, and mental health disorders. Tr. 518:15-519:12 (Winkelman).

86. Rifampicin treats "serious and disfiguring bacterial diseases," *id.* 519:12, including tuberculosis, DTX-129.6, leprosy, Tr. 519:7-12 (Winkelman), and Legionnaires' disease, *id.*

87. Fluvoxamine is an antipsychotic that treats "severe OCD" and "major depressive disorder." *Id.* 518:18-22.

88. Verapamil treats "a variety of heart arrhythmias, coronary artery disease" and a "variety of cardiac issues," *id.* 518:18-519:1, like angina, *id.* 252:18-253:1 (Combs).

89. Ciprofloxacin is indicated for treating typhoid fever, infectious diarrhea, and the plague. *Id.* DTX-128.5.

90. Dr. Combs agreed that fluvoxamine, verapamil, ciprofloxacin, and rifampicin treat serious conditions. Tr. 249:21-25 (Combs).

91. Dr. Combs agreed that rifampicin is indicated for the treatment of tuberculosis. *Id.* 246:22-247:1.

92. Dr. Combs agreed that fluvoxamine is indicated for the treatment of OCD. *Id.* 250:1-2.

93. Dr. Combs agreed that ciprofloxacin is indicated for the treatment of serious bacterial infections such as the plague. *Id.* 251:14-17.

94. Dr. Combs agreed that verapamil is indicated for the treatment of angina. *Id.* 252:18-253:1.

95. Discontinuing a patient's treatment with fluvoxamine, rifampicin, or ciprofloxacin can also pose serious health problems in addition to the underlying conditions these drugs treat.

96. Fluvoxamine's drug label, for example, warns "there have been reports of serious discontinuation symptoms" when patients stop taking fluvoxamine, including hypomania, anxiety, and "electric shock sensations." DTX-132.11.

97. The labels for rifampicin and ciprofloxacin, which again treat serious bacterial infections like leprosy and the plague, caution that "not completing the full course of therapy may . . . increase the likelihood that bacteria will develop resistance and will not be treatable by rifampicin[, ciprofloxacin] . . . or other antibacterial drugs in the future." DTX-129.9; DTX-128.42; Tr. 523:2-523:5 (Winkelman).

98. Dr. Combs acknowledged that stopping a patient's treatment with fluvoxamine, rifampicin, or ciprofloxacin can lead to serious health consequences. Tr. 246:23-247:5; 250:3-14 (Combs).

99. Dr. Combs agreed that discontinuing treatment of an active case of tuberculosis can have serious health consequences including death. *Id.* 247:2-5.

100. Given the serious health conditions these drugs treat (and the associated risks of prematurely terminating a patient's treatment with these drugs), physicians would not "discontinue" a Non-24 patient's treatment with fluvoxamine, verapamil, ciprofloxacin, or rifampicin. Tr. 519:13-523:5 (Winkelman).

101. If a Non-24 patient were already being treated with fluvoxamine, verapamil, ciprofloxacin, or rifampicin, physicians would avoid co-administering those drugs with tasimelteon by prescribing patients an alternative to tasimelteon. Tr. 519:13-523:5 (Winkelman).

102. Dr. Combs testified that prescribers would wait for patients to complete their course of treatment with fluvoxamine, verapamil, ciprofloxacin, or rifampicin and then begin on tasimelteon. Tr. 247:6-18 (Combs).

(b) There is not a single known instance where a prescriber encountered a Non-24 patient in need of tasimelteon who was already taking one of the claimed inducers or inhibitors.

103. In his 30-plus years of practice, Dr. Winkelman has never heard of a patient being treated with fluvoxamine, verapamil, ciprofloxacin, or rifampicin who had untreated non-24. Tr. 494:9-15; 516:5-9 (Winkelman).

104. Dr. Combs did not testify to any examples where patient with untreated non-24 was already being treated with fluvoxamine, verapamil, ciprofloxacin, or rifampicin. *See generally* Tr. 197:19-236:24 (Combs).

105. Tasimelteon first became available for physicians to prescribe in 2014, when the FDA approved Hetlioz, Vanda's brand-name version of tasimelteon. JTX-28.1 (Hetlioz Label).

106. Dr. Combs testified that while he has prescribed Hetlioz since its market entrance, he has never "discontinu[ed]" a Non-24 patient's treatment with

fluvoxamine, verapamil, rifampicin, or ciprofloxacin before prescribing Hetlioz to that patient. Tr. 248:8-249:25 (Combs).

107. Dr. Winkelman likewise confirmed he has never "seen any evidence that a single patient has had treatment with [fluvoxamine, verapamil, rifampicin, or ciprofloxacin] . . . discontinued in order to treat Non-24 with tasimelteon." Tr. 516:10-14 (Winkelman).

108. There may be around 10,000 Non-24 cases in the United States. *Id.* 552:20-553:1.

109. There is no evidence in the record that anyone has ever practiced the claims of the DDI patents. *See* Tr. 248:8-249:20 (Combs); Tr. 516:10-14 (Winkelman).

110. Dr. Winkelman testified that he has never heard of any instance of a physician discontinuing a patient's treatment with fluvoxamine, verapamil, ciprofloxacin, or rifampicin and then starting treatment with tasimelteon. Tr. 516:5-14 (Winkelman).

111. Vanda cites Dr. Polymeropoulos's testimony for its claim that there is "at least one" patient with Non-24 who "needed" both tasimelteon and rifampicin, D.I. 311, Vanda Op. Br. 12 (citing Tr. 158:14-20 (Polymeropoulos)).

112. In the cited testimony, Dr. Polymeropoulos testified that Vanda was "aware of" one instance of "coincident administration" of tasimelteon and

rifampicin. *Id.* 158:14-20. Dr. Polymeropoulos did not testify that this individual was suffering from Non-24.

2. Vanda failed to prove that Defendants specifically intend for physicians to practice the claimed steps of the DDI patents.

113. In relevant part, defendants' labels state:

> **7.1 Strong CYP1A2 Inhibitors (e.g., fluvoxamine)**
>
> Avoid use of tasimelteon in combination with fluvoxamine or other strong CYP1A2 inhibitors because of a potentially large increase in tasimelteon exposure and greater risk of adverse reactions.
>
> **7.2 Strong CYP3A4 Inducers (e.g., rifampin)**
>
> Avoid use of tasimelteon in combination with rifampin or other CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy.

JTX-30.3; JTX-33.4.

114. Sections 7.1 and 7.2 do not instruct, encourage, recommend, or promote how prescribers should go about avoiding co-administration of tasimelteon with fluvoxamine, verapamil, rifampicin, or ciprofloxacin. Tr. 517:12-518:14 (Winkelman).

115. These sections do not instruct, encourage, or recommend that physicians perform the claimed step of "discontinuing" a patient's treatment with fluvoxamine, verapamil, rifampicin, or ciprofloxacin. Tr. 517:12-14; 517:25-7 (Winkelman).

116. Defendants' labels leave it up to prescribers how to implement the warnings in Sections 7.1 and 7.2. Tr. 517:12-14; 518:4-7 (Winkelman).

117. In the event a physician chose to discontinue a patient's treatment with fluvoxamine, verapamil, rifampicin, or ciprofloxacin, that would be the result of a "patient-specific" determination in which the physician weighed the "risks and benefits" of "discontinuing" the patient's treatment with fluvoxamine, verapamil, rifampicin, or ciprofloxacin. *Id.* 518:4-14.

118. When asked on cross-examination whether the labels instruct physicians to "discontinue rifampicin and put that patient on tasimelteon," Dr. Combs stated that the label "doesn't say anything about stopping it totally." 247:6-18 (Combs).

119. Dr. Combs then explained his view that physicians will advise patients to finish their course of rifampicin treatment. *Id.*

120. Vanda states that Dr. Winkelman "agreed that it is a reasonable reading of the [defendants'] label[s] that physicians will discontinue fluvoxamine treatment, and switch the patient to another anti-psychotic." Vanda Op. Br. 10. In the cited testimony, Dr. Winkelman in fact said, "That is an option. That's not something a doctor would do." Tr. 547:20-548:8 (Winkelman).

III. Vanda has failed to adduce any probative evidence of secondary considerations of non-obviousness.

A. Vanda has failed to show that the purported secondary considerations of non-obviousness have a nexus to the claimed invention.

1. Vanda failed to carry its burden of demonstrating nexus.

121. From the eleven witnesses it proffered, Vanda did not elicit testimony that any alleged objective indicia are the direct result of unique characteristics of the claimed invention. *See, e.g.,* D.I. 312, Vanda PFF ¶¶ 157-166.

122. Vanda contends that the "Asserted Patents flow directly from Vanda's clinical studies." Vanda PFF ¶ 166. For this proposition, Vanda only cites the Asserted Patents themselves (JTX-1, -3, -4 & -6) and its clinical studies (JTX-110, PTX-2, -158, -185, & -187).

123. Bristol Myers Squibb ("BMS"), not Vanda, invented tasimelteon as a compound. Tr. 258:14-15 (Pandrapragada), 595:7-17 (Perni); JTX-12.23.

124. BMS, not Vanda, invented the use of tasimelteon to treat circadian rhythm disorders. Tr. 191:8-11 (Polymeropoulos); 724:13-725:2 (Emens); JTX-12.24.

2. BMS's '529 patent serves as a blocking patent.

125. U.S. Patent No. 5,856,529 ("'529 patent") issued in January 1999. Tr. 613:9-10 (Perni); JTX-12.1.

126. BMS was the applicant and is the assignee of the ’529 patent. Tr. 614:16-18 (Perni); JTX-12.1.

127. The only company with a license from BMS for the ’529 patent has been Vanda. Tr. 190:3-11 (Polymeropoulos).

128. The ’529 patent was the first patent to claim tasimelteon. Tr. 613:15-614:2 (Perni); JTX-12.23.

129. The ’529 patent covers the use of tasimelteon to treat circadian rhythm disorders. Tr. 191:8-11 (Polymeropoulos); 724:13-725:2 (Emens); JTX-12.24.

130. If someone wanted to make or use tasimelteon during the term of the ’529 patent, she would have needed to have a license to the ’529 patent. Tr. 1010:9-16 (Bergmeier); Tr. 190:18-191:5 (Polymeropoulos).

131. Vanda admits that the ’529 patent “would cover the use of tasimelteon for anything.” Tr. 1222:9-10.

B. Vanda’s evidence of secondary considerations is weak in any event.

132. Vanda asserts that a “short, sharp pulse” of tasimelteon is purportedly necessary to successfully entrain Non-24 patients. Vanda PFF ¶¶ 159-164.

133. To support its assertion that a “short, sharp pulse” is necessary to entrain patients, Vanda cites its own clinical study reports (JTX-58.47, PTX-187.56, PTX-185.70), briefing materials from an FDA committee meeting (JTX-110.139),

testimony from Dr. Polymeropoulos (Tr. 125:16-23, 137:4-15, 137:22-138:8, 138:16-24), and testimony from Dr. Combs (Tr. 233:4-20).

134. The cited pages of Vanda's clinical study reports present only graphs showing tasimelteon pharmacokinetics. JTX-58.47, PTX-187.56, PTX-185.70. The cited reports do not connect these pharmacokinetic profiles with, or state they are necessary to, tasimelteon's efficacy.

135. The cited page from the briefing material of the FDA committee meeting (JTX-110.139) does not connect tasimelteon's pharmacokinetic profile with its efficacy.

136. In the cited portions of his testimony, Dr. Polymeropoulos testified only that: (1) "tasimelteon, as administered, was able to entrain the circadian rhythm of blind people with Non-24," Tr. 125:16-23; (2) administering tasimelteon with food, with fluvoxamine, or with rifampicin would change the pharmacokinetic profile for tasimelteon, Tr. 137:4-15, 137:22-138:8, 138:16-24. Dr. Polymeropoulos did not demonstrate that any "short, sharp pulse" was necessary to tasimelteon's efficacy.

137. In the cited portions of Dr. Combs's testimony, he testified that combining tasimelteon with fluvoxamine could make tasimelteon less effective:

> So as we kind of touched on briefly, there's kind of that effect -- that short, sharp pulse for it to be effective. And so if you have spillover, you can actually -- it's no longer effective.

Tr. 233:15-18. But Dr. Combs himself never testified to the alleged premise that the "short, sharp pulse" was necessary to tasimelteon's efficacy.

1. The claimed inventions did not produce unexpected results.

(a) RE604 patent

138. Vanda has not shown that the invention claimed in the RE604 patent produced unexpected results. *Contra* Vanda PPF ¶¶ 168-182.

139. Dr. Emens explained that skilled artisans would have reasonably expected success in using 20 mg tasimelteon administered approximately one hour before bedtime to treat Non-24. Tr. 810:20-811:16.

140. By 1999—thirteen years before the priority date of the RE604 patent—BMS had obtained a patent that claimed the use of tasimelteon to treat circadian rhythm sleep disorders. JTX-12.24 (claim 14).

141. In 2007, Vanda disclosed in the published '244 publication that tasimelteon was a "specific and potent agonist of the MT1[] and MT2[] [] receptors" in the human brain that "demonstrate[d] potent chronobiotic activity" in the human body. DTX-41.2 ('244 publication); *see* Tr. 727:15-19 (Emens).

142. The '244 publication states that "[a]n oral dose of about 20 to about 50 mg [tasimelteon] is effective in treating sleep disorders when administered about 1/2 hour before sleep time." DTX-41.24; *see* Tr. 727:15-22 (Emens).

143. Vanda wrote patent claims directed specifically to the treatment of circadian rhythm sleep disorders with 20 to 50 mg of tasimelteon administered 0.5 hours before bedtime. DTX-41.25 (claims 1, 4, 5, 8); *see* Tr. 727:23-728:6 (Emens).

144. Non-24 is a circadian rhythm sleep disorder. Tr. 706:22-707:1 (Emens); *see also* DTX-16.7 (Hardeland) (noting that tasimelteon was "expected" to be useful in treating "entrainment difficulties"); PTX-473.7 (Vanda 2011 10-K).

145. Before the January 2012 priority date of the RE604 patent, skilled artisans knew that Vanda was running a Phase III clinical trial that involved administering 20 mg tasimelteon to Non-24 patients one hour before bedtime. *See* DTX-42.9-10; Tr. 796:24-797:12 (Emens); DTX-20.6.

146. Vanda would not likely have invested enormous resources into a Phase III trial and then designed the protocol to use a dose and timing of administration that skilled artisans would not have expected to work. Tr. 811:6-16 (Emens).

147. Contrary to Vanda's contention, Vanda PFF ¶¶ 168, concerns about spillover would not have been undermined skilled artisans' reasonable expectation of success. Skilled artisans had already concluded before January 2012 that 20 mg of tasimelteon (and higher doses as well) were effective at treating sleep disorders. Tr. 882:20-883:22 (Emens).

148. Any spillover 20 mg caused did not impair tasimelteon's efficacy. *Id.*

149. Vanda's expert Dr. Czeisler admitted that he was not aware of a single prior-art reference expressing any concern about a potential spillover effect with tasimelteon. Tr. 1199:2-6.

150. Dr. Emens explained that there is no milligram-to-milligram correlation between doses of tasimelteon and doses of melatonin. *See* Tr. 833:13-834:21 (Emens); *see also* PTX-5.8 (Dr. Emens' 2017 article noting that "we do not know how to compare doses of these two molecules").

151. The results of the Rajaratnam paper would have reinforced—rather than undermined—the skilled artisan's reasonable expectation of success. *Contra* Vanda PFF ¶¶ 170-171, 174. The Rajaratnam study involved patients who underwent an artificial five-hour phase advance—a "dramatic[]" advance, which would "model . . . something like jet lag from New York to London." Tr. 885:9-886:1 (Emens).

152. Rajaratnam found that, in that model, only the 100 mg dose of tasimelteon achieved a phase advance statistically different from placebo. PTX-816.7-8.

153. As Dr. Emens explained, in Rajaratnam, the 20 mg dose achieved a phase-shift that, while not statistically different from placebo, still exceeded one hour, *see* PTX-816.7 (Fig. 2.C), which would have been more than sufficient to treat Non-24. *See* Tr. 885:16-19 (Emens) ("I don't need to shift a full five hours to treat,

say, something like Non-24. At the most, I'm only going to need an hour phase shift which the 20-milligram dose gave me.").

154. Vanda's '244 publication, citing Rajaratnam's results, stated that the 20 mg was "preferable to an oral dose of about 100 mg." DTX-41.24.

155. A skilled artisan would not have looked at Rajaratnam "in isolation"; they would have "know[n] from Rajaratnam . . . I can get a 20-milligram phase shift" and "know[n] from [C]linical [T]rials that that's actually what [Vanda] chose in their clinical trial of Non-24." Tr. 885:20-24 (Emens).

156. Vanda's 2011 10-K was available to the public before 2012. Tr. 176:23-25 (Polymeropoulos); *see* PTX-473.6.

157. Vanda's 10-K characterized the results of the insomnia trials as "positive." It then noted that "the FDA granted orphan drug designation status for tasimelteon in a specific CRSD, N24HSWD in blind individuals without light perception." PTX-473.7.[1]

158. By January 2012, the prior art explicitly recognized that tasimelteon was likely to be successful in treating circadian rhythm sleep disorders such as Non-

[1] "The FDA grants orphan drug designation to drugs that may provide significant therapeutic advantage over existing treatments and target conditions affecting 200,000 or fewer U.S. patients per year. Orphan drug designation provides potential financial and regulatory incentives, including study design assistance, tax credits, waiver of FDA user fees, and up to seven years of market exclusivity upon marketing approval." PTX-473.7.

24. *See* DTX-20.6 (Lankford); DTX-41.2, 41.24-25 ('244 publication); DTX-16.7 (Hardeland).

159. Skilled artisans would have also expected success in administering tasimelteon shortly before bedtime because, as Dr. Czeisler admitted, tasimelteon has soporific properties (*i.e.*, it makes people sleepy). Tr. 1211:2-6 (agreeing that "one reason one might want to take 20 milligrams of tasimelteon near bedtime is to take advantage of the soporific effect that the drug has").

160. By January 2012, the prior art (and Vanda scientists) had stated that tasimelteon was expected to be effective in treating circadian rhythm sleep disorders generally, *see, e.g.*, JTX-91.1 (Vachharajani); DTX-41.2, 41.24-25 ('244 publication); DTX-16.7 (Hardeland), and Non-24 specifically, *see* DTX-20.6 (Lankford).

(b) '487 patent

161. Vanda has presented no evidence that taking tasimelteon without food is more effective at treating Non-24 than taking tasimelteon with food. *Contra* Vanda PFF ¶¶ 183-185.

162. The '487 patent specification does not contain any results of studies of tasimelteon in Non-24 patients; it talks only "about the effects of administering tasimelteon to sighted healthy individuals with or without food." Tr. 826:14-18 (Emens).

163. The ’487 patent incorporates by reference the specification of the RE604 patent, but the RE604 patent does not provide evidence that tasimelteon is more effective at treating Non-24 when administered without food. Tr. 827:11-828:4.

164. The only data in the RE604 patent are the results of the SET and RESET studies, in which all patients took the drug without food. *See* Tr. 827:11-18 (Emens).

165. Dr. Emens explained that, “to figure out tasimelteon is more effective at treating Non-24 when administered without food than it is administered with food,” one would “have to do a head-to-head trial. So you’d have to kind of do the study where you gave the tasimelteon to a group of patients with Non-24 with food and have some matched patients or crossover to the same patents where you then give it with and without food and see if one is more likely to cause treatment success than the other.” Tr. 827:19-828:3 (Emens).

166. There is no record evidence of a head-to-head trial studying whether tasimelteon is more effective at treating Non-24 when administered without food than it is administered with food.

167. The RE604 patent states three reasons to time the administration of tasimelteon near bedtime: “because it allows for avoidance of pre-sleep time soporific effects, because it allows for administration of higher doses that might have greater soporific effects, and because it allows for pharmacologic intervention at a

different phase of the sleep cycle than if it were administered earlier." JTX-1.40 (36:24-30). The RE604 patent does not recommend timing tasimelteon administration near bedtime so that it is taken without food.

168. There is no evidence in the record concerning the skilled artisan's expectation of what the effect would be of administering tasimelteon with food as compared to without food.

(c) '910 patent

169. Vanda has failed to show that tasimelteon's interaction with CYP3A4 inducers was unexpected. *Contra* Vanda PFF ¶¶ 186-188.

170. A skilled artisan would not have been able to "exclude a major role of CYP3A4 in the induced state," even in view of the Vachharajani paper's statement that "[n]o metabolism of [tasimelteon] was observed following incubation with . . . CYP3A4," Tr. 1116:13-20 (Greenblatt); *see* Vanda PFF ¶ 186 (quoting JTX-91.10).

171. Skilled artisans would not have excluded this role because "induction causes a massive increase in the amount of enzymes," meaning one "cannot exclude a major role of CYP3A4 in the induced state even if you can't detect it in the uninduced state." Tr. 1116:13-20 (Greenblatt).

172. Skilled artisans would have been particularly likely to suspect a potential interaction between tasimelteon and strong CYP3A4 inducers because it was known in the art that the structurally analogous compound ramelteon exhibited

a "large" drug-drug interaction with strong CYP3A4 inhibitors. *Id.* 1116:21-1117:13 (Greenblatt); *see also id.* 1050:20-1052:2 (Greenblatt).

(d) '829 patent

173. Vanda has failed to show that tasimelteon's interaction with CYP1A2 inhibitors was unexpected. *Contra* Vanda PFF ¶¶ 189-191.

174. A skilled artisan would have known that tasimelteon was metabolized by CYP1A2. Hardeland discloses that "tasimelteon was primarily metabolized by the CYP1A2 . . . isoenzyme[]." DTX-16.4 (citing Vachharajani); *see* Tr. 1036:3-16, 1049:3-25, 1100:2-9 (Greenblatt).

175. Hardeland further states that because "tasimelteon is metabolized by the CYP isoenzymes 1A2 . . . coadministration of any drug that inhibits one of these isoenzymes should be regarded with caution." DTX-16.6; Tr. 1049:3-1050:9, 1067:17-20, 1069:7-22 (Greenblatt).

176. Given Hardeland's disclosure, a skilled artisan would have expected that tasimelteon would interact with CYP1A2 inhibitors, such that it would be advisable to avoid co-administration of the two drugs. Tr. 1049:2-1050:13 (Greenblatt).

177. Ramelteon was a known melatonin agonist "closely related to tasimelteon." Tr. 1037:5-1037:8, 1040:13-24 (Greenblatt).

178. Ramelteon was known known to have a large drug-drug interaction with strong CYP1A2 inhibitors, such that co-administration of ramelteon and strong CYP1A2 inhibitors was contraindicated. Tr. 1044:12-1046:3 (Greenblatt).

179. Given what was known about ramelteon and its close similarity to tasimelteon, a skilled artisan would have expected a drug-drug interaction between tasimelteon and strong CYP1A2 inhibitors. Tr. 1037:5-6, 1038:25-1039:6, 1040:6-23, 1043:18-1046:3, 1116:24-1117:13 (Greenblatt), 1156:6-10 (Parkinson); JTX-93.4; DTX-16.2; JTX-35.2, 35.8, 35.10; JTX-92.1; DTX-28.9.

2. The claimed inventions did not fulfill a long-felt or unmet need.

180. The prior art contained unequivocal evidence that melatonin is effective at treating Non-24. JTX-146 (Hack 2003); *see* Tr. 716:2-721:4 (Emens).

181. The prior art's teachings were "clear": "melatonin could effectively entrain the circadian pacemaker and improve sleep . . . in blind individuals with Non-24." Tr. 1217:15-18 (Emens).

182. In 2007, "[t]he American Academy of Sleep Medicine issued two sets of practice parameters using two separate task forces and reached the same conclusion that that was the effective treatment for Non-24. And that was what was being recommended to sleep physicians in this country." Tr. 1217:19-24 (Emens).

183. Vanda did not invite any patients to speak at the FDA advisory committee meeting (cited by Vanda at Vanda PFF ¶¶193-201) whose Non-24 had been successfully treated with melatonin. *See* Tr. 1218:23-1219:8 (Emens).

184. Tasimelteon is not 100% effective in treating Non-24. *See* PTX-5.8.

185. The evidence suggests that tasimelteon is less effective than melatonin in treating Non-24. *See id.* (noting that the "entrainment rates for tasimelteon are a little lower than those for melatonin administered for 3-12 weeks" and that "[t]he true comparative efficacy of melatonin and tasimelteon for entrainment in non-24 awaits well-designed head-to-head trials"); *see also* Tr. 1217:25-1218:21 (Emens) (noting that the "lowest estimate" of the percentage of Non-24 patients melatonin entrains is about 60%).

3. The claimed inventions have not received significant industry praise.

186. Vanda has not presented evidence of industry praise of the specific inventions claimed in the asserted patents. *Contra* Vanda PFF ¶¶ 209-213.

4. There is no evidence that others tried and failed to arrive at the claimed invention.

187. There is no evidence that BMS—or anyone else—tried and failed to develop a method for using tasimelteon to treat Non-24. Tr. 189:10-12 (Polymeropoulos).

188. BMS did not fail to develop tasimelteon for shift-work disorder, *contra* Vanda PFF ¶ 216, but simply discontinued its shift-work disorder trial after the primary insomnia trials were unsuccessful. JTX-111.6, 9.

189. There is no evidence that BMS tried and failed to "develop a method of avoiding clinically significant interactions between tasimelteon and rifampicin," Vanda PFF ¶ 217.

/s/ Kaan Ekiner
Thomas Francella (No. 3835)
Kaan Ekiner (No. 5607)
COZEN O'CONNOR
1201 North Market Street, Suite 1001
Wilmington, DE 19801
(302) 295-2025
tfrancella@cozen.com
kekiner@cozen.com
Attorneys for Defendants Apotex Inc. and Apotex Corp.

OF COUNSEL:
Barry P. Golob
W. Blake Coblentz
Aaron S. Lukas
COZEN O'CONNOR
1200 Nineteenth Street N.W.
Washington, DC 20036
(202) 912-4800

/s/ Nathan R. Hoeschen
John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
Andrew E. Russell (No. 5382)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street
12th Floor
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
arussell@shawkeller.com
nhoeschen@shawkeller.com
Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

Keri L. Schaubert
COZEN O'CONNOR
3 WTC, 175 Greenwich Street
55th Fl.
New York, NY 10007
(212) 509-9400

OF COUNSEL:
J.C. Rozendaal
Deirdre M. Wells
William H. Milliken
Sasha Rao
Michael Bruns
Byron L. Pickard
STERNE, KESSLER, GOLDSTEIN
& FOX P.L.L.C.
1100 New York Avenue, N.W.
Suite 600
Washington, DC 20005
(202) 371-2600

Dated: May 17, 2022

CERTIFICATE OF COMPLIANCE

I hereby confirm that this document complies with the type and number limitations set forth in the Court's November 6, 2019 Standing Order and the Stipulation and Order Regarding Post-Trial Briefing (D.I. 305). I certify that this document contains 7889 words, which were counted using the word count feature in Microsoft Word, in 14-point Times New Roman font. The word count does not include the cover page, tables, or the counsel blocks.

/s/ Nathan R. Hoeschen
John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
Andrew E. Russell (No. 5382)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
arussell@shawkeller.com
nhoeschen@shawkeller.com
Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

Dated: May 17, 2022

CERTIFICATE OF SERVICE

I, Nathan R. Hoeschen, hereby certify that on May 17, 2022, this document was served on the persons listed below in the manner indicated:

BY EMAIL

Nicholas Groombridge
Eric Alan Stone
Josephine Young
Daniel J. Klein
Jennifer Rea Deneault
Michael F. Milea
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019
(212) 373-3000
ngroombridge@paulweiss.com
estone@paulweiss.com
jyoung@paulweiss.com
daklein@paulweiss.com
jdeneault@paulweiss.com
mmilea@paulweiss.com

Karen Jacobs
Derek J. Fahnestock
MORRIS, NICHOLS, ARSHT & TUNNELL LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
kjacobs@mnat.com
dfahnestock@mnat.com

/s/ Nathan R. Hoeschen
John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
Andrew E. Russell (No. 5382)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
arussell@shawkeller.com
nhoeschen@shawkeller.com
Attorneys for Defendant Teva Pharmaceuticals USA, Inc.